SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Indometacin 25 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 25 mg of indometacin

Excipients with known effect: Each capsule contains 150.0mg of lactose

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Hard gelatin capsule
Size 3, ivory opaque colour body & cap containing white to almost-white powder, imprinted "IND 25" in black ink on cap

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indometacin has non-steroidal analgesic and anti-inflammatory properties indicated for the following conditions:

- active rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, degenerative joint disease of the hip, acute musculoskeletal disorders; low back pain; acute gouty arthritis
- inflammation, pain and oedema following orthopaedic procedures
- treatment of pain and associated symptoms of primary dysmenorrhoea

4.2 Posology and method of administration

Posology
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

Adults

Dysmenorrhoea: Up to 75 mg a day, starting with onset of cramps or bleeding, and continuing for as long as symptoms usually last.

Acute gouty arthritis: 150 mg to 200 mg daily in divided doses until all symptoms and signs subside.

Elderly

The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for gastrointestinal bleeding during treatment with indometacin.

Paediatric population

Safety for use in children has not been established (see section 4.3).

Chronic conditions

In chronic conditions, starting therapy with a low dosage, increasing this gradually as necessary, and continuing a trial of therapy for an adequate period (in some cases, up to one month) will give the best results with a minimum of unwanted reactions. The recommended oral dosage range is 50 mg to 200 mg daily in divided doses.

Method of administration
For oral administration.

Indometacin Capsules should always be given with food or milk to reduce the chance of gastro-intestinal disturbance.

4.3 Contraindications

- Hypersensitivity to indometacin or any of the excipients (listed in section 6.1).
- NSAIDS are contraindicated in patients with angioneurotic oedema.
- NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin or other non-steroidal anti-inflammatory drugs.
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- History of gastrointestinal bleeding or perforation, related to previous NSAID therapy.
- Severe heart failure, hepatic failure and renal failure (see section 4.4).
- Patients with nasal polyps.
- During the third trimester of pregnancy (see section 4.6).
- Safety in children has not been established.
- Patients with coagulation defects.

4.4 Special warnings and precautions for use

In all patients
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

The use of indometacin with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

Elderly
The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).

Particular care should be taken with older patients who are more susceptible to side-effects from indometacin (see section 4.2).

Cardiovascular and cerebrovascular effects
Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy. Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for indometacin.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with indometacin after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking).

Cardiovascular, renal and hepatic impairment
In patients with reduced renal blood flow where renal prostaglandins play a major role in maintaining renal perfusion, the administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly, diabetes mellitus, extracellular volume depletion, congestive heart failure, sepsis or concomitant use of any nephrotoxic drug. Indometacin should be given with caution and renal function should be monitored in these patients. (See also section 4.3 Contraindications). Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

In patients with renal, cardiac or hepatic impairment, hypertension, heart failure or conditions predisposing to fluid retention, then caution is required since the use of NSAIDs could result in deterioration of renal function (see section 4.8).

The dose should be kept as low as possible and renal function should be monitored. NSAIDs may also cause fluid retention which could further aggravate these conditions.

It is reported that a few patients receiving non-steroidal anti-inflammatory drugs manifest borderline elevations in liver function test results. If these persist or worsen, or symptoms of liver disease, a rash or eosinophilia develop, treatment with indometacin should be stopped.

Respiratory disorders
Caution is required if administered to patients suffering from or with a previous history of bronchial asthma since NSAIDs have been reported to cause bronchospasm in such patients.

Gastrointestinal bleeding, ulceration and perforation
GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events. Rarely, intestinal ulceration has been associated with stenosis and obstruction. When GI bleeding or ulceration occurs in patients receiving indometacin, the treatment should be withdrawn.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcers, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available and, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. Combination therapy with protective agents (e.g.
misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

NSAIDs should be given with care to patients with a history of gastro-intestinal disease (ulcerative colitis, Crohn's disease), pre-existing sigmoid lesions (such as diverticulum or carcinoma), or the development of these conditions, as these conditions may be exacerbated (see section 4.8).

Gastro-intestinal disorders that occur can be reduced by taking indometacin with food or milk. They usually disappear on reducing the dosage; if not, the risks of continuing therapy should be weighed against the possible benefits. If gastro-intestinal bleeding or ulceration does occur, indometacin should immediately be discontinued.

Caution should be advised in patients receiving concomitant medications which could increase the risk of gastrotoxicity ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin or selective serotonin-reuptake inhibitors or anti-platelet agents (as indometacin can inhibit platelet aggregation and can exaggerate effects in patients with haemostatic defects), such as aspirin (see section 4.5).

SLE and mixed connective tissue disorders
In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8).

Impaired female fertility
The use of indometacin may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of indometacin should be considered.

Dermatological effects
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at a highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Indometacin should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

Patients should be carefully observed to detect any unusual manifestations of drug sensitivity.

Severe acute hypersensitivity reactions (e.g. anaphylactic shock) are very rarely observed. If first signs of a hypersensitivity reaction occur after taking indometacin, therapy must be discontinued.

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions with NSAIDs such as exacerbation of asthma (so called intolerance to analgesics / analgesics-asthma), Quincke's oedema (angioedema) or urticaria are more frequent than in other patients. Therefore, special precautions are recommended in such patients (readiness for emergency). This is also applicable to patients who are allergic to other substances, for example those with skin reactions, pruritus or urticaria.

Indometacin should be used cautiously in patients with impaired renal function, bleeding disorders, psychiatric disorders, epilepsy or Parkinsonism as it may tend to aggravate these conditions.

Indometacin may mask the signs and symptoms of infectious disease and this should be borne in mind in order to avoid delay in starting treatment for infection. Indometacin should be used with caution in patients with an existing, albeit controlled infection. Caution is advised with concomitant use of live vaccines.

Indometacin should be used with caution in patients with coagulation defects as indometacin can inhibit platelet aggregation. This effect may be exaggerated in patients with underlying haemostatic defects. Inhibition of platelet aggregation usually disappears within 24 hours of discontinuing indometacin.

Caution is required in post-operative patients as bleeding time is prolonged (but within normal range) in normal adults.

During prolonged therapy, periodic ophthalmic examinations are recommended, as corneal deposits and retinal disturbances have been reported. In patients with rheumatoid arthritis, eye changes may occur which may be related to the underlying disease or to the therapy. Therefore, in chronic rheumatoid disease, ophthalmological examinations at periodic intervals are recommended. Therapy should be discontinued if eye changes are observed.

Patients should be periodically observed to allow early detection of any unwanted effects on peripheral blood (anaemia), liver function (see section 4.8), or gastrointestinal tract especially during prolonged therapy.

Medication Overuse Headache (MOH)
After long term treatment with analgesics, headache may develop or aggravate. Headache caused by overuse of analgesics (MOH – Medication Overuse Headache) should be suspected in patients who have frequent or daily headaches despite (or because of) regular use of analgesics. Patients with medication overuse headache should not be treated by increasing the dose. In such cases the use of analgesics should be discontinued in consultation with a doctor.

Increases in plasma potassium concentration, including hyperkalaemia have been reported, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninaemic-hypoaldosteronism state.

Excipient(s) with known effect
This medicinal product contains lactose.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicinal product contains sodium.
This medicine contains 32 mg sodium (main component of cooking/table salt) in each capsule. This is equivalent to 1.6% of the recommended maximum daily dietary intake of sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Other analgesics including cyclooxygenase-2 selective inhibitors:
Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4.4). Use of indometacin with aspirin or other salicylates is not recommended as there is no enhancement of therapeutic effect while the incidence of gastro-intestinal side-effects risk is increased. Moreover, co-administration of aspirin may decrease the blood concentrations of indometacin. There is a risk of increased side effects and haemorrhage if given with ketorolac.

Quinolone antibiotics:
Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions. Skin reactions and neurotoxicity have been reported with ciprofloxacin.

Anti-coagulants:
NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4). Although clinical studies suggest that indometacin does not influence the hypoprothrombinaemia induced by anticoagulants, patients also receiving anticoagulants should be closely observed for alterations of the prothrombin time. The risk of ulceration and bleeding is increased with indometacin (see section 4.4).

Anti-diabetic agents:
The effect of sulfonylureas may be increased by NSAIDs.
Isolated cases of metabolic acidosis when given with metformin.
Isolated cases of an influence on blood glucose levels have been reported after administration of indometacin, which required dose adjustment of the antidiabetic medication. Therefore, monitoring of the blood glucose values is recommended as a precaution.

Anti-epileptics:
Indometacin may enhance the effects of phenytoin.

Anti-hypertensives:
Reduced anti-hypertensive effect. Indometacin may acutely reduce the anti-hypertensive effect of beta-blockers due partly to indometacin's inhibition of prostaglandin synthesis. Patients receiving dual therapy should have the antihypertensive effect of their therapy reassessed. Therefore, caution should be exercised when considering the addition of indometacin to the regimen of a patient taking any of the following antihypertensive agents: alpha-adrenergic blocking agents, ACE inhibitors, beta-adrenergic blocking agents, angiotensin-2-receptor antagonists, hydralazine or nifedipine. Hyperkalaemia has also been reported with ACE inhibitors.

Anti-platelet agents:

Increased risk of gastrointestinal bleeding (see section 4.4). Increased risk of bleeding with taking clopidogrel. Indometacin can inhibit the platelet aggregation, an effect which disappears within 24 hours of discontinuation; the bleeding time may be prolonged and may be exaggerated in patients with an underlying haemostatic defect.

Anti-psychotics:
Indometacin may cause severe drowsiness if taken with haloperidol.

Anti-virals:
Pharmacokinetic changes have been recorded with zalcitabine and indometacin. Risk of indometacin toxicity with taking ritonavir, avoid concomitant use.

Zidovudine, Ibuprofen:
Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Muscle Relaxants:
NSAIDs may reduce excretion of baclofen with a potential for increased risk of toxicity.

Benzodiazepines:
There is an increased risk of dizziness with diazepam and indometacin.

Cardiac glycosides:
NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate and increase plasma glycoside levels. Indometacin given concomitantly with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin. Therefore, when indometacin and digoxin are used concomitantly, serum digoxin levels should be closely monitored.

Ciclosporin:
Concomitant administration of ciclosporin may lead to increased risk of nephrotoxicity. Administration of NSAIDs taken concomitantly with ciclosporin has been associated with an increase in ciclosporin-induced-toxicity, possibly due to decreased synthesis of renal prostacyclin. NSAIDs should be used with caution in patients taking ciclosporin and their renal function should be monitored carefully.

Corticosteroids:
Increased risk of gastrointestinal ulceration or bleeding (see section 4.4). If the patient is receiving corticosteroids concomitantly, a reduction in dosage of these may be possible but should only be effected slowly under supervision.

Cytotoxics:
Caution should be used with cyclophosphamide as acute water intoxication has been reported.

Desmopressin:
Effect potentiated by indometacin.

Diflunisal:
Co-administration of diflunisal with indometacin increases the plasma levels of indometacin by about a third, with a concomitant decrease in renal clearance. Fatal gastro-intestinal haemorrhage has occurred. The combination should not be used.

Diuretics, potassium-sparing diuretics and aldosterone antagonists:
Reduced diuretic effect. Indometacin may reduce the diuretic and antihypertensive effect of thiazides and furosemide in some patients. Indometacin may cause blocking of the

furosemide-induced increase in plasma renin activity. May increase the risk of nephrotoxicity of NSAIDs. Indometacin and triamterene should not be administered together since renal failure may be induced.
There is a possible increased risk of hyperkalaemia when NSAIDs are given with *Potassium-sparing diuretics and aldosterone antagonists*. Monitoring of potassium levels is recommended.

ACE inhibitors and angiotensin II receptor antagonists:
May increase the risk of nephrotoxicity of NSAIDs. There is a possible increased risk of hyperkalaemia when NSAIDs are given with these agents. Monitoring of potassium levels is recommended.

Drosperidone:
There is a possible increased risk of hyperkalaemia when NSAIDs are given with this agent. Monitoring of potassium levels is recommended.

Lithium:
Decreased elimination of lithium. Indometacin is an inhibitor of prostaglandin synthesis and therefore the following drug interactions may occur; indometacin may raise plasma lithium levels and reduce renal lithium clearance in subjects with steady-state plasma lithium concentrations causing a possible increased risk of toxicity. At the onset of such combined treatment, plasma lithium concentration should be monitored more frequently.

Methotrexate:
Decreased the elimination of methotrexate. Simultaneous use should be undertaken with caution.

Mifepristone:
NSAIDs should not be used for 8-12 days after mifepristone administration as they can reduce its effect.

Muromonab-CD3:
Indometacin may cause a significant rise in the incidence of psychosis and encephalopathy in patients receiving both these drugs.

Penicillamine:
There is a possible increased risk of nephrotoxicity if penicillamine is given with an NSAID.

Phenylpropanolamine:
Hypertensive crises have been reported due to oral phenylpropanolamine alone and, rarely, to phenylpropanolamine given with indometacin. This additive effect is probably due partly to indometacin's inhibition of prostaglandin synthesis. Caution should be exercised when indometacin and phenylpropanolamine are administered concomitantly.

Probenecid:
Co-administration of probenecid may increase plasma levels of indometacin. When increases in the dose of indometacin are made under these circumstances, they should be made cautiously and in small increments. Avoid concomitant use.

Selective Serotonin Reuptake Inhibitors (SSRIs):
Increased risk of gastrointestinal bleeding (see section 4.4).

Tacrolimus:
Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Tiludronic acid:
Indometacin increases the bioavailability of tiludronic acid.

Vancomycin:
Studies in premature neonates being treated for patent ductus arteriosus have shown that concomitant administration of indometacin and vancomycin may have additive nephrotoxic effects. As such, caution is advised during concurrent or subsequent use of indometacin and vancomycin, as indometacin may increase the risk of vancomycin related toxicities. Where possible, monitor vancomycin levels and adjust the vancomycin dose and/or dosing interval accordingly.

Vasodilators:
Possible increased risk of bleeding with NSAIDs.

Venlafaxine, clopidogrel, erlotinib, iloprost, pentoxifylline (oxpentifylline) and sibutramine:
When indometacin is taken with these agents there is an increased risk of bleeding.

If possible, consumption of alcohol should be avoided during use of indometacin as it may increase the risk of gastrointestinal haemorrhaging.

The dexamethasone suppression test may give false negative results.

4.6 Pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

From the 20th week of pregnancy onward, indometacin use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimesters of pregnancy, indometacin should not be given unless clearly necessary. If indometacin is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to indometacin for several days from gestational week 20 onward. Indometacin should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the

foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, indometacin is contraindicated during the third trimester of pregnancy (see section 4.3 or 5.3).

Breast-feeding

In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breast-feeding.

Fertility

For impaired female fertility, see section 4.4.

4.7 Effects on ability to drive and use machines

Undesirable central nervous effects such as dizziness, drowsiness, fatigue, vertigo and visual disturbances are possible after taking NSAIDs. Alcohol or other centrally acting medicines may increase these effects. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Blood and lymphatic system disorders: Blood dyscrasias (such as thrombocytopenia, neutropenia, leukopenia, agranulocytosis, aplastic and haemolytic anaemia), bone marrow depression, petechiae, epistaxis, ecchymosis, purpura and disseminated intravascular coagulation may occur infrequently. Some patients may develop anaemia secondary to obvious or occult gastro-intestinal bleeding, Appropriate blood determinations are recommended.

Immune and system disorders: Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, rhinitis or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema (swelling of the face, tongue, and inner larynx with constriction of the respiratory passages), and, more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Metabolism and nutrition disorders: Hyperglycaemia, hyperkalaemia and glycosuria have been reported rarely.

Nervous system disorders: Headache and dizziness are common side effects. Starting therapy with a low dose and increasing gradually minimises the incidence of headache. These symptoms frequently disappear on continued therapy or reducing the dosage, but if headache persists despite dosage reduction, indometacin should be withdrawn. Other CNS effects include reports of aseptic meningitis (especially in patients with existing auto-immune

disorders, such as systemic lupus erythematosus or mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4), depression, vertigo, dizziness, fatigue, dysarthria, coma, cerebral oedema, confusion, nervousness, anxiety and other psychiatric disturbances, depersonalisation, hallucinations, drowsiness, convulsions and aggravation of epilepsy, peripheral neuropathy, paraesthesia, involuntary movements, insomnia and Parkinsonism. These effects are often transient and abate or disappear upon reducing dosage or stopping treatment. However, occasionally, severe reactions may require stopping therapy.

Eye disorders: Visual disturbances, blurred vision, optic neuritis and orbital and periorbital pain are seen infrequently. Corneal deposits, retinal or macular disturbances have been reported in some patients with rheumatoid arthritis on prolonged therapy with indometacin, and ophthalmic examinations are desirable in patients given prolonged treatment.

Ear and labyrinth disorders: Tinnitus or hearing disturbance/auditory defects (rarely deafness) have been reported.

Cardiac disorders: There have been reports of oedema, hypertension, hypotension, tachycardia, chest pain, arrhythmia, palpitations and cardiac failure. Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Vascular disorders: Flushing has been reported.

Respiratory, thoracic and mediastinal disorders: Pulmonary eosinophilia. There may be bronchospasm in patients with a previous history of bronchial asthma or other allergic reactions.

Gastro-intestinal disorders: The most commonly-observed adverse events are gastrointestinal in nature. Nausea, anorexia, vomiting, epigastric discomfort or abdominal pain, dyspepsia, melaena, haematemesis, constipation or diarrhoea all have been reported. Less frequently, gastritis has been observed; more rarely, stomatitis, ulcerative stomatitis, flatulence, ulceration at any point in the gastrointestinal tract (even with resultant stenosis and obstruction), bleeding (even without obvious ulceration or from a diverticulum) and perforation of pre-existing sigmoid lesions (such as diverticulum or carcinoma) have occurred; and increased abdominal pain or exacerbation of the condition in patients with ulcerative colitis or Crohn's disease (or the development of this condition), intestinal strictures and regional ileitis have been rarely reported (see section 4.4). Pancreatitis has been reported very rarely. Peptic ulcers, perforation and gastro-intestinal, sometimes fatal, particularly in the elderly, may occur (see section 4.4). If gastro-intestinal bleeding does occur, treatment with indometacin should be discontinued. Gastro-intestinal disorders which occur can be reduced by giving indometacin with food, milk or antacids.

Hepatobiliary disorders: Abnormal liver function, cholestasis. Rarely hepatitis and jaundice (associated with some fatalities). Borderline elevations of one or more liver tests may occur, and significant elevations of ALT (SGPT) or AST (SGOT) trials. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations such as rash or eosinophilia occur, indometacin should be stopped.

Skin and subcutaneous tissue disorders: Pruritus, urticaria, angioneurotic oedema, angiitis, photosensitivity, erythema nodosum, rash, exfoliative dermatitis, erythema multiforme, hair loss, sweating and exacerbation of psoriasis have all been reported infrequently. Bullous reactions including Stevens Johnson syndrome and toxic epidermal necrolysis (very rare).

Musculo-skeletal, connective tissue and bone disorders: Muscle weakness and acceleration of cartilage degeneration.

Renal and urinary disorders: Elevation of blood urea, haematuria, proteinuria, and renal insufficiency have all been reported. Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and renal failure. In patients with renal, cardiac or hepatic impairment, caution is required since the use of non-steroidal anti-inflammatory drugs may result in deterioration of renal function. The dose should be kept as low as possible and renal function should be monitored.

Reproductive system and breast disorders: Vaginal bleeding, breast changes (enlargement, tenderness, gynaecomastia).

Investigations: False-negative results in the dexamethasone suppression test (DST) in patients being treated with indometacin have been reported. Thus, results of this test should be used with caution in these patients.

Laboratory tests
Borderline elevations of one or more liver tests may occur, and significant elevations of ALT (SGPT) or AST (SGOT) have been seen in less than 1% of patients receiving therapy with NSAIDs in controlled clinical trials. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations such as rash or eosinophilia occur, indometacin should be stopped.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms
Symptoms include headache, nausea, vomiting, epigastric pain or abdominalgia, gastrointestinal bleeding, rarely diarrhoea, disorientation, vertigo, excitation, coma, drowsiness, dizziness, tinnitus, fainting, occasionally spasms or convulsions. In cases of significant poisoning acute renal failure and liver damage are possible.

Management
Patients should be treated symptomatically as required. The stomach should be emptied as quickly as possible if the ingestion is recent and correction of severe electrolyte abnormalities may need to be considered.

Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Good urine output should be ensured. Renal and liver function should be closely monitored. Patients should be observed for at least four hours after ingestion of potentially toxic amounts. Frequent or prolonged convulsions should be treated with intravenous diazepam.

Depending on the condition of the patient, close medical observation and nursing care may be required. The patient should be followed for several days because gastro-intestinal ulceration

and haemorrhage have been reported as adverse reactions of indometacin. Use of antacids may be helpful.

The plasma elimination of indometacin is biphasic with the half-life of the terminal plasma half-life phase between 2.6 and 11.2 hours.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Anti-inflammatory and anti-rheumatic products.
ATC code: M01AB01

Indometacin is a non-steroidal analgesic, antipyretic and anti-inflammatory agent. It is an inhibitor of prostaglandin synthetase.

The analgesic effects are attributed to both central and peripheral effect, which are distinct from its anti-inflammatory activity.

Indometacin is one of the most potent inhibitors of the prostaglandin-forming cyclo-oxygenase. Like colchicine, it inhibits motility of polymorphonuclear leukocytes. Like many other of the aspirin-like drugs, indometacin uncouples oxidative phosphorylation in supratherapeutic concentrations and depresses the biosynthesis of mucopolysaccharides.

5.2 Pharmacokinetic properties

Absorption: Indometacin is rapidly and almost completely absorbed from the gastro-intestinal tract on oral administration, and peak plasma concentrations are reached in ½ to 2 hours. Absorption is slowed but remains virtually complete when taken with food.

Distribution: More than 90% is bound to plasma proteins. It is distributed into the synovial fluid, the CNS and the placenta. Low concentrations have been found in breast milk.

Metabolism: It is metabolised primarily in the liver by O-demethylation and N-deacylation and undergoes glucuronidation and enterohepatic circulation.

Elimination: Mainly excreted in the urine. Lesser amounts are found in the faeces. Indometacin is also excreted in breast milk in small amounts.

5.3 Preclinical safety data

Administration of indometacin to experimental animals at doses of 0.1-1.94 times the MRHD resulted in: i) maternal toxicity and death, ii) increased pre- and post-implantation loss. iii) increased embryotoxicity, foetal resorptions and foetal death, and iv) increased spontaneous abortion.

In pregnant mice and rats, indometacin treatment (during organogenesis) induced developmental defects including retarded foetal ossification and skeletal malformations at doses of 0.02-0.95 times the MRHD.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium Stearate
Sodium Lauryl Sulfate
Primojel
Lactose

Capsule Shell (size 3)
Erythrosine E127
Quinoline Yellow E104
Titanium Dioxide E171
Gelatin NF XVI

6.2. Incompatibilities

None known.

6.3 Shelf Life

3 years

6.4 Special precautions for storage

Store below 30°C. Store in the original package in order to protect from light.

6.5 Nature and Contents of Container

PVC/Aluminium blister pack containing 28, 30, 56, 60, 84, 90, 100, 112, 250, 500 or 1000 capsules

HDPE container containing 28, 30, 56, 60, 84, 90, 100, 112, 250, 500 or 1000 capsules.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Tillomed Laboratories Ltd
220 Butterfield
Great Marlings
Luton
LU2 8DL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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